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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/715,725
Filing Date: November 16, 2000
Appellant(s): LUO ET AL.

James S. Keddie
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 14, 2006 appealing from the Office action mailed August 10, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

No evidence is relied upon by the examiner in the rejection of the claims under appeal.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(1) Claims 26-27, 29-30, 32 are rejected under 35 USC 112, first paragraph as failing to comply with the enablement requirement. That is, the claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. This is enablement rejection and is set forth in the Office Action mailed August 10, 2005, Section 3, pages 2-10.

As set forth therein, Examiner reviews the contemplated uses for ING2 proteins suggested by the specification and clearly provides reasons why one would not know how to use the claimed ING2 protein, SEQ ID NO:8, for the uses contemplated in the specification.

The specification teaches that ING2 proteins are useful for (i) screening for bioactive agents capable of interfering with the binding of a cell cycle protein and IAPs, (ii) screening for bioactive agents that modulate the activity of a cell cycle protein/cell cycle, (iii) screening for a bioactive agents capable of modulating apoptosis, (iv) activating p53 binding site controlled promoters, (v) inducing or preventing cell proliferation in cells, (vi) diagnosis, treatment, prevention of cell cycle associated disorders, preferably cancer.

(i') As drawn to screening for bioactive agents capable of interfering with the binding of a cell cycle protein and IAPs, there is no teaching either in the specification or the art of record that SEQ ID NO:8 is in fact a cell cycle protein. Although the specification suggests that the ING2 proteins are cell cycle proteins based on sequence identity of ING2 and ING 1 which the specification teaches is art recognized as a cell cycle protein (see below), the specification also teaches that cell cycle proteins can be identified by substantial amino acid sequence identity (greater than 75% to 98% identity) to SEQ ID NO:8 and thus it would appear that as defined by the specification, ING1 is not a cell cycle protein. If the ING1 gene product, acknowledged by the art to be a cell cycle protein, is not a cell cycle protein as defined by the specification and the designation of the ING2 isoform as a cell cycle protein is based on homology to the ING1 gene product,

then SEQ ID NO:8 could not be a cell cycle protein and one would not know how to use SEQ ID NO:8 for any of the functions associated with cell cycle proteins. Further, there is no teaching as to which IAP might be bound by SEQ ID NO:8 or even whether or not SEQ ID NO:8 binds to any IAP, thus one could not predict that the claimed polypeptide could be used for screening for bioactive agents capable of interfering with the binding of a cell cycle protein and IAP.

The specification provides insufficient guidance with regard to these issues drawn and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to use the claimed invention with a reasonable expectation of success.

(ii') As drawn to screening for bioactive agents that modulate the activity of a cell cycle protein/cell cycle, given that there is no objective evidence presented in the specification or art of record drawn to any activity of SEQ ID NO:8, given the differences in activity of the isoforms with homology to SEQ ID NO:8 that have been characterized, given the teachings of Bowie et al, Bork, Burgess et al, Lazar et al drawn to the unpredictability of protein chemistry, one could not predict, based only on the teaching of the specification as originally filed and the art of record, that SEQ ID NO:8 could be used to modulate the activity of a cell cycle

protein/cell cycle or even how to use this modulation if it were to occur. The specification provides insufficient guidance with regard to these issues drawn and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to use the claimed invention with a reasonable expectation of success.

(iii') As drawn to screening for a bioactive agents capable of modulating apoptosis, no evidence has been presented providing a nexus between SEQ ID NO:8 or any other isoform with homology to SEQ ID NO:8 and apoptosis. Further, even if such a nexus were to be established given the differences in activity of the isoforms with homology to SEQ ID NO:8 that have been characterized, given the teachings of Bowie et al, Bork, Burgess et al, Lazar et al drawn to the unpredictability of protein chemistry, one could not predict, based only on the teaching of the specification as originally filed and the art of record, that SEQ ID NO:8 could be used to screen for agents capable of modulating apoptosis. The specification provides insufficient guidance with regard to these issues drawn and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to use the claimed invention with a reasonable expectation of success.

(iv') As drawn to activating p53 binding site controlled promoters, the submitted Shiseki et al reference (Can. Res., 2003, 63:2373-2378) clearly demonstrates that an isoform with sequence homology to SEQ ID NO:8, wherein the isoform is 100% identical to SEQ ID NO:8 except for 13 amino acids at its N-terminal end, does not activate p53 binding site controlled promoters in the absence of p53 wherein activation is not in fact activation of the promoter, but rather physical activation of p53 by recruitment of cofactors which enhance acetylation of p53. Although the specification includes Figure 12 which is described at page 5 of the specification as "a graph depicting p53 activation by ING2" wherein some of the isoforms of SEQ ID NO:8 exemplified in Figure 12 (which do not include SEQ ID NO:8) are involved in "induction" in the presence and absence of p53 there is no discussion in the specification of what is in fact exemplified in Figure 12. There is no teaching of which system, that is, *in vitro* or *in vivo* is used to make the determination, for example, whether transfection and resulting constitutive overexpression of constituents was used to determine that the exemplified ING2 isoforms were involved in "induction" or activation or in what tissue or system this finding might be relevant. In the absence of this information, it is not possible for the skilled practitioner to evaluate the information in this figure and it cannot be predicted from this information that the characterized ING2

isoforms are in fact activating p53 binding site controlled promoters. Given that SEQ ID NO:8 is not even disclosed in Figure 12 and given the unpredictability of protein chemistry as set forth previously and above, given that the Shiseki molecule does not activate p53 binding site controlled promoters in the absence of p53 wherein activation is not in fact activation of the promoter, but rather physical activation of p53 by recruitment of cofactors which enhance acetylation of p53, it cannot be predicted based only on the information set forth in the specification as originally file and the art of record that SEQ ID NO:8 functions to activate a p53 binding site controlled promoter.

Further, neither the specification nor the art of record provides information drawn to which p53 binding site controlled promoter SEQ ID NO:8 might activate. Given the teachings of Szak et al (Mol. Cel. Biol., 2001, 21:3375-3386) drawn to the complexity of the p53 cell cycle protein cascade, given the ever-increasing number of p53 downstream targets being identified, given the differential kinetics of p53 binding to p53 consensus binding sites which results in differential activation of those promoters, given this well known diversity, it could not be predicted which of the p53 binding site controlled promoters SEQ ID NO:8 might activate or what the effect of that activation might be.

The specification provides insufficient guidance with regard to these issues drawn and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to use the claimed invention with a reasonable expectation of success.

(v')(vi') As drawn to inducing or preventing cell proliferation in cells, and diagnosis, treatment, prevention of cell cycle associated disorders, preferably cancer, the basis for these contemplated uses appears to be the sequence identity of SEQ ID NO:8 to ING1 and the apparent designation of ING2 proteins, SEQ ID NO:8, as cell cycle proteins. However, the identity of ING1 to SEQ ID NO:8 is only 12.3% and given the teachings of Bowie et al, Bork, Lazar et al Burgess et al, all of record, one could not predict based only on the sequence identity that SEQ ID NO:8 shares function with ING1 or if it does share functions, what those functions might be. Further, it is noted, that although the specification teaches that the art recognizes that ING1 is a cell cycle protein and specifically teaches that cell cycle proteins can be identified by substantial amino acid sequence identity (greater than 75% to 98% identity) to SEQ ID NO:8, it would appear that ING1 is in not a cell cycle protein. If the ING1 gene product, acknowledged by the art to be a cell cycle protein, is not a cell cycle protein as defined by the specification and

the designation of the ING2 isoform as a cell cycle protein is based on homology to the ING1 gene product, then SEQ ID NO:8 could not be a cell cycle protein and one would not know how to use SEQ ID NO:8 for any of the functions associated with cell cycle proteins.

As drawn specifically to diagnosis, treatment, prevention of cell cycle associated disorders, neither the specification nor the art of record provide a nexus between SEQ ID NO:8 and any disorder. In the absence of any nexus provided to any disorder, it could not be predicted that SEQ ID NO:8 is in fact associated in any way with any disorder and one would not know how to diagnose, treat or prevent any disorder with the claimed polypeptide.

As drawn specifically to the claims 27, 30 and 32 drawn to SEQ ID NO:8 or a molecule with 95% identity to SEQ ID NO:8 increasing activity of a promoter having a p53 binding site when introduced into a mammalian cell, the specification does not disclose or contemplate this activity.

The specification provides insufficient guidance with regard to these issues drawn and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to use the claimed invention with a reasonable expectation of success.

(2) Claims 27, 30, 32 are also rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification as originally filed. This is a new matter rejection and is set forth in the Office Action mailed August 10, 2005, Section 4, pages 10-12.

As stated therein, the limitation of "a recombinant ING2 protein, comprising an amino acid sequence having at least 95% identity to the contiguous sequence set forth in SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell" has no clear support in the specification and the claims as originally filed. Although Appellant cited support for the newly added claimed limitations at page 7, line 7, page 33, lines 5-6, page 37, line 4 of the specification, the cited support was drawn only to "ING2 activates p53 binding site controlled promoters in the presence or absence of p53" (p. 7, line 7) and drawn to activating "p53 binding site controlled promoters" (p. 33, lines 5-6), and drawn to "activation of p53 binding site controlled promoters" (p. 37, line 3). After careful review it is clear that none of the cited support is drawn to the new, broadly claimed invention wherein the claims now read on a recombinant ING2 protein which increases activity of a promoter having a p53 binding site, wherein the newly added claim limitation broadens the scope of the claimed invention. The newly claimed invention is

different than the invention taught in the specification and therefore represents new matter because it is clear from a review of the specification in general and the cited support in particular, that the newly claimed limitation was neither taught nor contemplated in the specification as originally filed.

Further, as drawn specifically to claim 27, none of the cited support is drawn to a recombinant ING2 protein comprising an amino acid sequence having at least 95% sequence identity to the contiguous sequence set forth in SEQ ID NO:8 which functions as claimed. Again it is clear that the newly claimed limitation was neither taught nor contemplated at the time the application was filed and the newly amended claims represent new matter. Thus, the subject matter claimed in claims 27, 30 and 32 broadens the scope of the invention as originally disclosed in the specification.

(3) Claims 27 is also rejected under 35 USC 112, first paragraph as lacking an adequate written description. This rejection is set forth in the Office Action mailed August 10, 2005, Section 5, pages 12-16.

As set forth therein, examiner points to the Lilly and Enzo standards for the written description requirements. Examiner states that the specification as originally filed does not meet the Enzo standard because it does not describe the physical or chemical characteristics of a recombinant ING2 protein comprising an

amino acid sequence having at least 95% identity to SEQ ID NO:8 that increases activity of a promoter having a p53 binding site nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Further, Examiner states that the specification as originally filed does not meet the Lilly standard because although the specification provides description of several variants of SEQ ID NO:8, all of which have an identical 200 amino acid sequence, wherein the specification states that they all have a single identical p53 modulatory domain that lies within amino acids 20 to 299, for the reasons set forth previously and below, these variants do not provide a representative number of species composing the genus claimed or define structural features commonly possessed by members of the genus that distinguish them from others, wherein a definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

(4) If Appellant were able to overcome the rejections set forth above, Claims 27 is also rejected under 35 USC 112, first paragraph because the specification, while being enabling for a recombinant ING2 protein comprising SEQ ID NO:8 does not reasonably provide enablement for a recombinant ING2 protein having at least 95% identity to the contiguous sequence set forth in SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53

binding site. This rejection is set forth in the Office Action mailed August 10, 2005, Section 8, pages 17-19.

As set forth therein, given the unpredictability of protein chemistry as taught by Bowie et al, Burgess et al, Lazar et al, given that there is no teaching or guidance drawn to the amino acids that are critical to the claimed invention, one would not know how to make the claimed recombinant ING2 protein comprising an amino acid sequence having at least 95% sequence identity to the contiguous sequence set forth in SEQ ID NO:8, wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site.

(10) Response to Argument

(1) With regard to the enablement rejection of claims 26-27, 29-30 and 32, Appellant argues at page 5 of the Brief that the instant rejection is grounded on a lack of utility basis and that claims 26-27 are not rejected under 35 USC 101 and points to MPEP 2164.071.A which states that Office personnel should not impose a 35 USC 112, first paragraph rejection grounded on a lack of utility basis unless a 35 USC 101 rejection is proper. The argument has been carefully considered but has not been found persuasive because, as set forth above, the grounds of rejection are drawn to a careful analysis of why one, based on the information in the specification and in the art of record would not know how to use the claimed

invention. In addition, a review of MPEP 2164 reveals that MPEP specifically states-in-part that;

> If an appellant has disclosed a specific and substantial utility for an invention and provided a credible basis supporting that utility, that fact alone does not provide a basis for concluding that the claims comply with all the requirements of 35 U.S.C. 112, first paragraph. For example, if an appellant has claimed a process of treating a certain disease condition with a certain compound and provided a credible basis for asserting that the compound is useful in that regard, but to actually practice the invention as claimed a person skilled in the relevant art would have to engage in an undue amount of experimentation, the claim may be defective under 35 U.S.C. 112, but not 35 U.S.C. 101. To avoid confusion during examination, any rejection under 35 U.S.C. 112, first paragraph, based on grounds other than "lack of utility" should be imposed separately from any rejection imposed due to "lack of utility" under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph.

Thus, for the reasons set forth previously and above, Examiner has found that to actually practice the invention as claimed, a person skilled in the relevant art would have to engage in an undue amount of experimentation and the claims are found to be defective under 35 USC 112, first paragraph, for the reasons set forth previously and above, but not defective under 35 USC 101. In order to avoid confusion, this rejection based on grounds other than "lack of utility" has been imposed.

Appellant argues at page 6 of the Brief that in attempting to establish this rejection, the Examiner asserts that there is no nexus between SEQ ID NO:8 and either ING2B or ING2C showing activation of p53, a well known tumor

suppressor and thus SEQ ID NO:8 has no use and points to the action mailed August 8, 2003, page 2-3 and page 4, lines 21-23.

The argument has been considered but has not been found persuasive because a review of the rejection at page 3, lines 10-11 reveals that Appellant is mischaracterizing Examiner's statements and that contrary to Appellants argument, Examiner never asserted that due to the lack of nexus between SEQ ID NO:8 and SEQ ID NOS: 4 AND 6 that "SEQ ID NO:8 has no use". What was stated in fact was that given the lack of nexus, it was not possible to evaluate Appellant's arguments. Further, a review of the rejection at page 4, lines 21-23 reveals that Appellant is again mischaracterizing Examiner's statements and that contrary to Appellants arguments, Examiner never asserted that due to the lack of nexus between SEQ ID NO:8 and SEQ ID NOS: 4 AND 6 that "SEQ ID NO:8 has no use". What was stated is that there was no teaching in the art of record that either ING2b or ING2c are in fact SEQ ID NO:8.

Appellant argues that these grounds for enablement rejection are substantially identical to the grounds to support the prior utility rejection under 35 USC 101 which was withdrawn in view of Appellant's arguments earlier in prosecution and that maintenance of a rejection under 35 USC 112, first paragraph on the same grounds that were the basis of a rejection under 35 USC 101 is

inconsistent with the law and the Patent Office requirement for Examiners to efficiently examine applications and avoid "piecemail" prosecution" .

The argument has been considered but has not been found persuasive because the claims were previously rejected, not only under 35 USC 101 but also under 35 USC 112, first paragraph and although the rejection under 35 USC 101 was withdrawn, the claims are not enabled for the reasons set forth. Thus contrary to Appellant's argument, the prosecution is not a piecemeal prosecution.

Appellant states that SEQ ID Nos 2, 4, 6, 8, 10 as well as p28ING5 (the molecule of Shiseki et al) are splice variants encoded by the same gene and share a 200 amino acid domain and as shown in the instant specification and in Shiseki et al each of ING2b, ING2c and p28 ING4 regulate expression from p53 binding site promoters. In view of this data and the high relatedness of the members of the ING2 family, Appellant argues at page 6 of the Brief that one of skill would reasonably conclude that SEQ ID NO:8 has uses that are enabled by the instant specification, for example in screening assays for identifying agents that modulate p53 activity and the cell cycle.

The argument has been carefully considered but has not been found persuasive because Examiner has clearly demonstrated the differences in activity of the characterized splice variants, has clearly set forth that SEQ ID NO:8 has not

been characterized and that for the reasons set forth previously and above, it could not be predicted that the invention will function as contemplated. Further, as drawn to claims 27, 30, 32, Appellant is arguing limitations not recited in the claims as currently constituted since the claims as currently constituted are drawn to SEQ ID NO:8 protein which "increases activity of a promoter having a p53 binding site". For the reasons set forth previously and above, the claimed invention is not enabled.

(2) With regard to the new matter rejection of claims 27, 30 and 32, Appellant argues at page 7, section 2 of the Brief that according to the MPEP, an objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed?" and further argues that a claim amendment need not be *in haec verba* in order for the disclosure to satisfy the written description requirement.

This argument has been carefully considered but is not found persuasive because the issue raised is not whether the description clearly allows persons of ordinary skill in the art to recognize that he or she invented what is claimed, but rather that the newly added limitation has no clear support in the specification and the claims as originally filed. Further, a review of MPEP 2163(I)(B) reveals clearly

that while there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. It is clear that the newly added broad limitations are not supported by the specification expressly, implicitly or inherently since the teachings of the specification are clearly drawn to ING2 proteins that activate p53 binding site controlled promoters and not to the newly claimed recombinant ING2 proteins which increase activity of a promoter having a p53 binding site.

Appellant argues at page 7 of the Brief that extensive and explicit support for ING2 proteins that increase the activity of a promoter having a p53 binding site can be found in several places in the specification. At page 8 of the Brief, Appellant points to the specification at page 7, lines 8-9 which states that "ING2 activates p53 binding site controlled promoters in the presence or absence of p53" and points to the specification at page 33, lines 5-6 which states that cell cycle proteins "activate p53 binding site controlled promoters" and points to the specification at page 37 line 3 which states that assay employing an ING2 polypeptide can include measuring "activation of p53 binding site controlled promoters" and finally points to Figure 12 which shows data demonstrating that ING2 protein increases transcriptional activation by p53 in a mammalian cell. The arguments have been carefully considered but have not been found persuasive

because as drawn to the cited support at pages 7, 33, 37 as set forth in the Office Action mailed August 10, 2005, page 7, section 2, the cited support is not drawn to increasing activity of a promoter having a p53 binding site, but rather is drawn to activation of p53 binding site controlled promoters. After careful review it is clear that none of the cited support is drawn to the new, broadly claimed invention wherein the claims now read on a recombinant ING2 protein which increases activity of a promoter having a p53 binding site, wherein the ING2 protein is not required to activate a p53 binding site controlled promoter. The claimed invention broadens the scope of the invention taught and contemplated in the specification as originally filed.

Further, as drawn specifically to claim 27, it is noted that Appellant does not address the rejection of the claim under the new matter written description provision of 35 USC 112, first paragraph wherein the rejection is drawn to ING2 proteins having 95% identity to SEQ ID NO:8 which increase activity of a promoter having a p53 binding site when introduced into a mammalian cell. It is clear that nothing is the cited support is drawn to a recombinant ING2 protein, comprising an amino acid sequence having at least 95% sequence identity to SEQ ID NO:8 which functions as claimed. Thus, as set forth previously and above, the

newly amended claims broaden the scope of the invention as originally disclosed in the specification.

(3) With regard to the written description rejection of claim 27 Appellant argues at page 9 of the Brief that the fact pattern of the instant case falls squarely into the fact pattern of Example 14 of the Synopsis of Written Description Guidelines. Specifically, Appellant points out that Example 14 of the Guidelines describes a scenario very similar to that currently under examination, wherein the Example is drawn to "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A->B." Appellant argues that the language of the instant claim and the claim of Example 14 is almost identical wherein both recite a specific sequence and a functional activity. Appellant further points out that like the fact pattern of the instant application, Example 14 provides a polypeptide sequence and contemplates but does not exemplify variants of an amino acid sequence. At page 10 of the Brief, Appellant points out that like the fact pattern of the instant application, Example 14 provides an assay for measuring the activity of the protein. In particular, Appellant argues that the instant specification teaches that SEQ ID NO:8 has IAP binding activity at page 33 lines 4-5 and teaches that SEQ ID NO:8 has p53-modulatory activity at Figure 12 and page 7, lines 8-10 and that the specification provides

detailed methods of how IAP binding activity (at page 42, lines 16-27) and p53 modulatory activity (at Figure 12) can be assayed.

The argument has been carefully considered but has not been found persuasive because, contrary to Appellant's arguments, the fact patterns of Example 14 and the instant fact pattern are not the same. Although Appellant is correct that the language of the instant claim and the claim of Example 14 are almost identical wherein both recite a specific sequence and a functional activity, unlike the fact pattern of Example 14, the specification does not provide an assay for the claimed functional activity. Although Appellant clearly states that SEQ ID NO:8 has both IAP binding activity and p53-modulatory activity and points to assays disclosed in the specification for testing IAP binding activity at page 42 and p53 modulatory activity in Figure 12, it is noted that the specification does not teach that SEQ ID NO:8 in particular has IAP binding activity and Figure 12 does not disclose SEQ ID NO:8. Further, the functional limitation for which patent protection is sought is drawn to neither to IAP binding activity and nor p53 modulatory activity but rather is drawn to a recombinant ING2 protein having at least 95% sequence identity to the contiguous sequence set forth in SEQ ID NO:8, wherein said recombinant protein **increases activity of a promoter having a p53 binding site**" (emphasis added). Appellant has not pointed to an assay for this

function and a review of the specification did not reveal an assay for this function. Further, as set forth previously and above, the specification as originally filed does not meet either the Lilly or the Enzo standards for written description. Although Appellant argues at page 10 of the Brief that five similar ING2 isoforms, corresponding to SEQ ID NOS 2, 4, 6, 8, 10 are described in the specification and the alignment of the five sequences is set forth in Figure 11, it is noted that SEQ ID NO:8, ING2D is not disclosed in Figure 11. Further, although the sequence alignment of Figure 11 demonstrates identity between the proteins disclosed, it is noted that Appellant does not argue that these related isoforms contain a structure correlated to the claimed function or that these related isoforms increase activity of a promoter having a p53 binding site. Thus, although these isoforms might be related to SEQ ID NO:8, they do not support the written description of the claimed invention because they are not known to and have not been shown to be representative of the claimed genus and no structure that is correlated with the claimed function has been identified.

Finally, the specification does not provide a disclosed correlation between any structure within SEQ ID NO:8 and the claimed functional limitation, does not describe structural features common to the members of the genus, which features constitute a substantial portion of the genus, does not provide a representative

number of variants having at least 95% identity with SEQ ID NO:8 that increase activity of a promoter having a p53 binding site or define structural features commonly possessed by members of the genus that distinguish them from others.

At page 11 of the Brief, Appellant argues that, the reversal of this rejection would be consistent with recent decisions by the Board of Patent Appeals and Interferences and points specifically to *Ex parte Bandman*, BAPI Appeal No. 2004-2319 (2004) and *Ex Parte Sun* BAPI Appeal No. 2004-1993 (2003) wherein the genus claims that are the subject of these decisions were supported by disclosure of a single representative species. Since the instant claims are supported by five examples, the instant claims should well satisfy criteria used by the Board for withdrawing this type of rejection.

The argument has been considered but has not been found persuasive because a review of the Board decisions drawn to *Ex parte Bandman* and *Ex Parte Sun* reveal that the fact patterns of those two cases are very different from the fact pattern found in the instant case.

In particular, a review of *Ex parte Bandman* reveals that although the Board did decide that the recitation of a single sequence met the Written Description Guidelines for the genus of the polypeptides claimed, unlike the instantly claimed **recombinant** (emphasis added) ING2 protein having 95% identity to SEQ ID

NO:8, the claimed invention of *Ex parte Bandman* was drawn to **naturally occurring amino acid sequences** (emphasis added) that are at least 95% identical to a wild-type sequence. The court found that "through the process of natural selection, nature will have determined the appropriate amino acid sequences". In the instant application the claim is clearly drawn to recombinant polypeptide, it is not drawn to "naturally occurring amino acid sequences" and thus nature will not have determined the appropriate amino acid sequences.

In particular, a review of *Ex Parte Sun* reveals that although the Board did decide that the recitation of a single sequence met the Written Description Guidelines for the genus of polypeptides claimed, this decision was based not only on the disclosure of the specific chemical structure of a polynucleotide comprising the coding sequence set forth in SEQ ID NO:1, and the teaching on how to test for Wee1 activity but also on the teaching of the areas of the Wee1 gene that can be altered without disturbing substrate recognition. The Board states that "What is evident from the record is those of ordinary skill in the art were aware that most of the variations in amino acid sequences of Wee1 are in the amino terminus, while the carboxy end of the genes are relatively conserved. Those of skill in the art were also aware that "the carboxyl terminus and the central portion of the Wee1 protein ..... contain the protein kinase domains and sequence crucial for substrate

recognition and catalysis. Thus, those of ordinary skill in the art would have recognized from reading the disclosure that the inventors had invented the isolated Wee1 having the specific nucleotide and amino acid sequences and variations of these sequences with mutations in described specific areas of Wee1, while avoiding the introduction of mutations in other regions. This teaching, coupled with the ability to test for functional mutants with the assays provided for in the specification, supports appellants' position." However, unlike the fact pattern in *Ex Parte Sun*, the instant fact pattern does not provide an assay for testing the claimed function of the instant invention, does not provide information drawn to a correlation between the structure and function of the claimed polypeptide.

Thus, contrary to Appellant's arguments, the fact pattern of the instant case is not consistent with the fact pattern of the cited Board decisions wherein the genus claims that were subject to the decisions were supported by disclosure of a single representative species.

Given the above, it is clear that the instantly claimed invention does not meet the standard of Example 14 of the Guidelines because no assay for the functional limitation is taught and does not meet the standard of Lilly or Enzo because no structure/function relationship has been taught and only a single

representative species has been taught and structural features commonly possessed by members of the genus that distinguish them from others are not defined.

(4) With regard to the scope of enablement rejection of claim 27 Appellant argues at page 12 of the Brief that the instant specification, combined with what is already known about the related ING1 protein, which is a highly characterized protein and has a function similar to ING2, provides sufficient guidance to which amino acids could be changed in ING2 in order for it to remain functional and thus no undue experimentation would be required to practice what is being claimed. Appellant argues that with regard to ING2 protein domains that are important for ING2 function, a skilled person would look towards Figure 11 of the specification (which discloses the alignment of isoforms of ING2 proteins and ING1 proteins, but not the claimed SEQ ID NO:8) and what is known about the structure and function of the highly related ING1 protein.

The argument has been considered but has not been found persuasive because although Figure 11 indeed does show alignment of isoforms of ING2 proteins and ING1 proteins, SEQ ID NO:8, which is ING2D is not included in the figure and therefore a skilled person could not look towards Figure 11 of the specification in order to determine domains that are important for the function of ING2D, SEQ ID NO:8 as claimed.

Appellant further argues that ING1 is highly characterized and has a role in apoptosis that appears to be similar to that of ING2 (and points to page 7 of the specification for the role of ING1 in apoptosis) and that residues that are conserved between two or more proteins in this alignment are highlighted. This alignment shows several regions that are conserved between the various ING proteins including in particular, several conserved amino acids at the C-terminus of the protein and a large region of amino acids at the C-terminus of the protein starting with the "DPNEPTY..." and finishing at "....TTKPKGKW".

The argument has been considered but has not been found persuasive because although Appellant argues that ING1 and ING2 have similar apoptotic activity and regions of amino acid identity, the functional limitation for which patent protection is sought is not drawn to apoptosis activity but rather is drawn to a recombinant ING2 protein having at least 95% sequence identity to the contiguous sequence set forth in SEQ ID NO:8, wherein said recombinant protein **increases activity of a promoter having a p53 binding site**" (emphasis added). Thus, Appellant is arguing limitations not recited in the claim as currently constituted.

Appellant further argues at page 12 of the Brief that since ING1 and ING2 are functionally similar and contain several regions of conserved amino acids at

their C-termini, a skilled person would instantly recognize that these domains **may** (emphasis added) be important for function of ING proteins. Appellant further argues that given that these domains are conserved among the different ING2 isoforms themselves further suggests to the skilled person that these domains are less preferred for introduction of amino acid changes and a skilled person would generally avoid making amino acid changes in these regions when designing ING2 variants that are at least 95% to SEQID NO:8. Thus with the knowledge that ING1 and ING2 have apoptosis activity and have conserved domains, a skilled person would, for example swap domains from ING1 to ING2 (i.e. SEQ ID NO:8) with an expectation that the resultant protein would retain an apoptosis activity.

The argument has been considered but has not been found persuasive because Appellant continues arguments drawn to apoptosis activity and therefore is arguing limitations not recited in the claim as currently constituted.

Appellant argues at page 13 of the Brief that upon viewing the instant specification, particularly Figure 11, and the references cited on page 7, lines 22-24, Helbing, et al., Cancer Res., 57(7):1255-8 (1 997); Garkavtsev, et al., Nat Genet., 14(4):415-20 (1 996); Shimada, et al., Cytogenet Cell Genet., 83(3-4):232-5 (1 998) regarding the structure/function relationship of ING proteins one would

have knowledge of the prior art and would apply this knowledge in the production of claimed ING2 variants.

The argument has been considered but has not been found persuasive because a review of the Helbing et al reference, reveals that the methods disclosed are not drawn to structure/function relationships of the ING1 protein and no information drawn to the relationship of any structure to any function of the ING1 protein is disclosed. Similarly, a review of the Garkavtsev et al reference reveals that the methods disclosed are not drawn to structure/function relationships of the ING1 protein and no information drawn to the relationship of any structure to any function of the ING1 protein are disclosed. Finally a review of the Shimada et al reference also reveals that the methods disclosed are not drawn to structure/function relationships of the ING1 protein and no information drawn to the relationship of any structure to any function of the ING1 protein are disclosed. Given that none of the cited art is drawn to the relationship of any structure to any function of the ING1 protein one would not be able to apply this knowledge in the production of the claimed ING2 variants.

Appellant particularly argues that Zeremski, discusses several amino acids that are conserved between ING proteins and indicates that the conserved C-terminal domain is a PHD DNA binding domain and that most of the conserved

amino acids of Zeremski's sequence alignment are also indicated as being conserved in the alignment of Figure 11. While not relied upon to make this assertion, Zeremski confirms that the conserved amino acids identified in Figure 11 are found in ING proteins and assigns an art-recognized domain name and function to the conserved C-terminal region.

The argument has been considered but has not been found persuasive because a careful review of the Zeremski et al reference reveals that although the ING1 proteins comprise a conserved C-terminal domain and that the C-terminal domain is a PHP DNA binding domain, and some of these conserved residues are found in the ING2 isoforms disclosed in Figure 11, the reference is drawn only to activation and inhibition of p53 and is not drawn to the claimed function, that is the function of increasing activity of a promoter having a p53 binding site, thus once again Appellant is arguing limitations not recited in the claims as currently constituted. Further, the prior art reference clearly demonstrates the unpredictability of the art of protein chemistry wherein Zeremski et al clearly teach that, despite the conserved nature of the PHP DNA binding domain, one isoform of ING1 cooperates with/activates p53 while the other inhibits p53 activity (see abstract). Thus it is clear that differences in amino acid constitution of the proteins, despite conserved amino acids, will lead to different functions. Further, Zeremski

et al teach that a similar type of regulation involving alternative initiation leading to variability is found in other tumor suppressor genes namely BRCA1, APC and INK4, wherein this regulation is associated with the generation of proteins with different functions (p. 32180, col 1). Given the teachings of Zeremski et al, of record, Bowie et al of record, Burgess et al of record, Lazar et al of record, it is clear that based only on sequence identity, one could not reliably predict which variants of SEQ ID NO:8 would function as claimed and it could not be predicted which of the regions of identity are critical to the function to increase activity of a promoter having a p53 binding site

At page 14 of the Brief, Appellant argues that a skilled person would recognize a large number of amino acids in an ING2 protein having the sequence of SEQ ID NO:8 that may be substituted and reasonably expect that these substitutions would have no effect on its function. The argument has been considered but has not been found persuasive given that Zeremski et al specifically teach the unpredictability of the art wherein despite conserved amino acids, differences in amino acid sequence lead to differences in function. Thus, given the teachings of Zeremski et al in combination with the teachings of Bowie et al of record, Burgess et al of record, Lazar et al of record, given that the specification provides no teachings drawn to amino acid residues critical to the claimed

function, the effect of alteration of the amino acids of SEQ ID NO:8, despite conservation in amino acid sequence, cannot be predicted and the specification does not teach how to predictably make the claimed invention with a reasonable expectation of success.

At page 15 of the specification, Appellants argue that since all ING proteins shown in Figure 11 have a conserved function, since a consensus sequence that shows conserved amino acids is disclosed, that a skilled person would recognize that in order to make ING2 variants, a skilled person would instantly recognize a large number of amino acids in SEQ ID NO:8 may be substituted and reasonably expect that these substitutions would have no significant effect on ING2 function. The argument has been considered but has not been found persuasive given the teachings of Bowie et al of record, Burgess et al of record, Lazar et al and the teachings of Zeremski et al and the lack of guidance drawn to the amino acids critical to the claimed function.

At page 15 Appellant notes that the specification provides working examples of five ING2 isoforms, ING2A, 2B, 2C, 2D, 2E, corresponding to SEQ ID Nos 2,4, 6, 8, 10, respectively wherein ING2a, ING2B, ING2C, ING2E share 87.6%, 94.2%, 94.2% and 81.8% identity to SEQ ID NO:8. Appellant argues that considering that each of ING2A, ING2B, ING2C, ING2D and ING2E bind IAP

and can induce p53 expression (see Figure 12 of the instant specification) a skilled person would reasonably expect ING2 variants with at least 95% identity to SEQ ID NO:8 to have an activity similar to that of SEQ ID NO:8.

The argument has been considered but has not been found persuasive because once again Appellant is arguing limitations not recited in the claims as currently constituted since the claims are not drawn to either induction of p53 expression or IAP binding. Further, it is noted that induction of p53 expression is not contemplated in the specification and that it does not appear from the information in the specification that Figure 12 is drawn to the induction of p53 expression. In particular, the only teaching in the specification drawn to Figure 12 is the statement at page 5 that "Figure 12 is a graph depicting p53 activation by ING2". Although a review of figure 12 reveals bars drawn to "induction" it does not appear, and in fact cannot be determined, that the induction disclosed is drawn to p53 expression. Further, it is also noted that contrary to Appellant's arguments, even if the induction disclosed were drawn to p53 expression, Figure 12 does not show that each of ING2A, ING2B, ING2C, ING2D and ING2E can induce p53 expression, since it is clear that ING2A does not induce anything other than a normal variation about control and neither ING2D nor ING2E are disclosed in Figure 12.

Finally Appellant argues that in summary, the specification provides adequate evidence that one can substantially modify the amino acid sequence of an ING2 protein without loss of function since ING1 which has as little as 81.8% identity to an ING2 protein has a function similar to that of ING2, a skilled person would recognize that ING2 proteins with at least 95% sequence identity to an ING2 protein could be made and used without undue experimentation.

The argument has been considered but has not been found persuasive because for the reasons set forth previously and above, one can not substantially modify the amino acid sequence of SEQ ID NO:8 with a reasonable expectation of successfully producing a modified SEQ ID NO:8 which increases activity of a promoter having a p53 binding site because the amino acids critical to this function have not been defined. Further, it is noted that contrary to Appellant's argument, ING1 does not have 81.8% identity to an ING2 protein, but as set forth previously and above, has only 12.3% identity to SEQ ID NO:8. Further, it is noted that the only protein disclosed in the specification which has "as little as" 81.8% identity to another protein is SEQ ID NO:2, ING2A which has 81.8% identity to SEQ ID NO:8, wherein no comparison of any activity of SEQ ID NO:2 is made with SEQ ID NO:8, wherein Figure 12 clearly demonstrates that the functionality SEQ ID NO:2 is different from that of SEQ ID NO:4, which is different from that of SEQ

ID NO:6, clearly demonstrating that differences in amino acid sequence result in differences in functionality and wherein it is clear that the specification as originally filed does not teach how to make the claimed variant SEQ ID NO:8 polypeptides with a reasonable expectation of success.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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